# Special Feature

# Reflections on Errors in Neonatology III. The ''Experienced'' Years, 1970 to 2000

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## INTRODUCTION

The first two articles of this series dealt with errors in neonatology, which occurred during the ''Hands Off'' years (1920 to 1950) and the ''Heroic'' years (1950 to 1970). From 1970 on, we call the ''Experienced'' years. This period is characterized by a refinement of the methods and treatments introduced in the earlier periods. The algorithms of neonatal intensive care become similar around the world. Some new treatments are studied before being generally accepted. Randomized controlled trials are more common. Organizations such as the FDA and committees of the American Academy of Pediatrics are more involved in assessing problems and making recommendations. Institutional research review boards become more authoritative, and there seem to be fewer errors. Perhaps we have learned from these past experiences. However, that may not be true. The increased complexity of our care and of our patients may simply make errors less apparent.

In this article, we will discuss problems with infant formulas, ''inactive'' ingredients in drugs, erythromycin, steroids and conclude with an analysis of the causes of errors and ways to avoid errors in the future.

## INFANT FORMULA ERRORS

Breast-feeding has always been accepted as the best feeding method for infants. And there have always been reasons for seeking substitutes. Wet nursing was used for many centuries and reached a peak in Western Europe in the 17th century. However, that practice was not universally approved because many felt the wet nurse could pass her own bad traits through the milk.[1] Animal milks were substituted, but with the migration of populations to the city as the industrial revolution progressed, the supply of near-at-hand fresh milk was scarce. The milk that was available soured quickly and was frequently adulterated. Paps and panadas were substituted.[2] These were thick, cereal-based, milk-less concoctions, which were not appropriate calorically. This method of feeding contributed to the extraordinarily high infant mortality rates. In the 18th century, about half the infants born alive in London died before reaching 2 years of age.[3] An infant formula was developed by von Liebig in Germany in the 1860s. A variant of this formula was sold by Nestlé in this country in 1873.[4]

The history of modern infant formulas begins with the determination of the chemical composition of milk by Biedert in Germany and Meigs in the US in the 1890s. Biedert, considering the casein of cow's milk indigestible, recommended the dilution of milk. This approach was the origin of the ''percentage'' method of preparing an infant milk feeding, which approached human milk in the percent composition of protein, fat and carbohydrate. Dr. Rotch of Boston developed his method of ''percentage feeding'' in which very gradual changes were made in these percentages used to prepare the feeding.[5] From his practice of calculating feedings came the word ''formula'' for prepared milk feedings. In 1910, Dr. Jerome Leopold returned from Germany with the opinion that the use of dextrin and maltose in formulas improved their digestibility. He convinced the Mead-Johnson Company to produce Dextri-Maltose, which was unveiled at the 1912 American Medical Association Convention.[4]

In 1915, Dr. H.J. Gerstenberger and H.O. Ruh began clinical testing of a formula containing fats approximating those in human milk. This testing was carried out at the Babies' Dispensary and Hospital in Cleveland. The formula was synthetic milk adapted (SMA) and was subsequently produced by The Laboratory Products Co., later bought by Wyeth Laboratories. SMA was made generally available in 1921.[4]

The Moores and Ross Milk Company in Columbus, Ohio, acquired the Franklin Brewery building at the onset of Prohibition. In collaboration with Alfred Bosworth, a milk chemist, a new infant formula called Franklin Infant Food was introduced. The name was subsequently changed to Similac and in 1928 sales were begun.[6]

## NEO-MUL-SOY FORMULA

One of the swiftest responses to an error began on July 26, 1979 when three cases of failure to thrive and metabolic alkalosis were

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reported to the Center for Disease Control (CDC). All three infants were being fed a soy-based formula, Neo-Mul-Soy. On July 30, CDC investigators surveyed a sample of pediatric nephrologists in the US and found an additional 15 cases and another 16 cases from other sources. All the infants had received either Neo-Mul-Soy or Cho-Free, formulas produced by the same company. By August 2, the company had analyzed the suspect formulas, met with the FDA, halted manufacture, ordered a recall, and notified health-care professionals throughout the country about the problem.[7] Fortunately, the children recovered quickly when supplemented with another formula or chloride.

The most complete discussion of the epidemic is contained in an article by Dr. Shane Roy, the originator of the initial report to the CDC.[8] The metabolic alkalosis was caused by the renal effects of chloride deficiency. In the ascending limb of the loop of Henle, sodium reabsorption is passive, dependent on the active reabsorption of chloride. Therefore, chloride deficiency decreases sodium reabsorption in this segment and increases sodium delivery to the distal tubule where sodium is reabsorbed in exchange for hydrogen and potassium ions. Increased sodium delivery and reabsorption in the distal tubule increases the excretion of hydrogen ions, generating bicarbonate and resulting in metabolic alkalosis.

The factors leading to the deficiency of chloride in the formula are very interesting. In the 1950s and 1960s, the concern surfaced that hypertension might result from increased sodium intake in infancy.[9] Although this correlation was never verified, in 1971 the American Academy of Pediatrics (AAP) recommended that the ''salt content'' of infant foods be reduced.[10] The salt added to baby foods and formulas up to that time was based on adult taste preferences. In 1976, the AAP made recommendations for lowered sodium content in formulas.[11] Following that recommendation, Syntex Laboratories reformulated Neo-Mul-Soy, intending the chloride content of the formula be 6 meq/l. Federal regulations did not require that chloride content of formula be monitored and inadvertently many of the Syntex formula batches had less than 2 meq/l of chloride. Also, in that time period, infant feeding practice included avoiding solid foods until at least 6 months of life. In 1977, the baby food industry quit adding salt to infant foods. A publication by Gerber Products Co. in 1978 details the history of this change and expressed concern that this change might lead to sodium insufficiency in stressed infants.[12] Apparently, the combination of a chloride-deficient formula and the low salt content of baby foods led to this epidemic.

The infants with chloride deficiency also had growth failure as shown in Figure 1. The decrease in head growth led to the question of brain growth and jeopardized intellectual development. The CDC began a registry of cases that included 141 infants. Syntex estimated that 20,000 children in the US had received the chloride-deficient formula. Malloy[13] presents a fascinating article reviewing the results of independent follow-up studies, and the history and results of a federally funded program to measure these children's subsequent development. The final results showed some specific

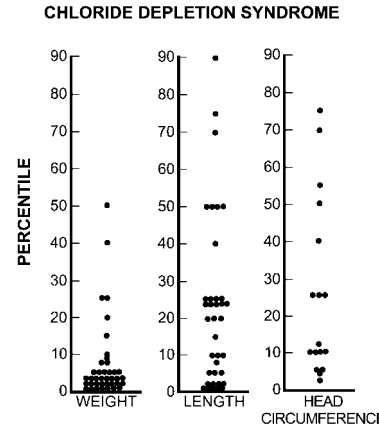


**Figure 1.** Percentile measurements at the time of diagnosis, for weight, length and head circumference in 39 reported infants with metabolic alkalosis secondary to ingestion of chloride-deficient formula. Reproduced with permission (Ref [8]), p238.

differences between affected, nonaffected and control infants, but the confounding variables make these differences questionable. In the conclusions of this review, Dr. Malloy states, ''The follow-up of infants exposed to chloride-deficient formulas was a complex study influenced by the difficulties inherent in all follow-up studies and complicated by the political and litigious nature of the subject.''

## PREMATURE INFANT FORMULAS

The development of specific formulas for premature infants began with studies in the 1940s and 1950s, which compared breast-milk-fed premature babies with babies fed on cow-milk-based formulas.[14] The cow milk formulas contained more protein, calcium and phosphorus, and infants receiving these formulas grew more rapidly than those on breast milk. Therefore, the new premature infant formulas were designed with more protein, calcium and phosphorus than previous formulas and more calories per ounce. Mead-Johnson introduced Enfamil Premature Formula in 1966 (Mead-Johnson, personal communication). In 1978, Ross Laboratories introduced Similac 24 LBW for premature infant feeding.[15]

With the increased popularity of powdered infant formulas after World War II, reports of lactobezoars (milk bezoars) were first seen in 1959.[16] The term bezoar comes from the Arabic or Persian term meaning antidote to poison. A bezoar is an accumulation of foreign material in the intestinal tract, usually the stomach. In ancient times, bezoars taken from animal stomachs were thought to have magical powers against poisons and diseases.[17] Bezoars in infants were attributed to the improper preparation of the formula and/or dehydration. In 1970, Levkoff et al.[18] described a lactobezoar in a premature infant receiving Similac 24 with iron.

In 1979, reports from California, Iowa and Indiana revealed 24 cases (going back to 1977) of lactobezoars in premature infants, almost all of whom had received the premature infant formulas manufactured by Ross Laboratories and Mead-Johnson.[19–21] The infants were predominantly under 1500 g birth weight and

developed the lactobezoar in the first 2 weeks of life while feeding was progressing well. The feeding method was usually continuous nasogastric infusion. The infants presented with signs of intestinal obstruction, which often resolved after 24–48 hours of no enteral feedings. Figure 2 shows an intraluminal mass in the attributed to a lactobezoar.[22] This problem led, almost immediately, to the practice of beginning feedings with diluted premature infant formulas.

It was fairly clear that this epidemic related to the use of these 24 kcal/ounce premature formulas. What was not clear was what aspect of the formulas led to the lactobezoar formation. Suggestions included the higher protein and calcium concentration, the casein predominance (~80%) of the protein leading to higher curd tension and the medium-chain triglyceride in the formulas leading to delayed gastric emptying.[23] Also considered was the fact that feedings were being instituted earlier in premature infants since the premature formulas were introduced. Continuous nasogastric feedings had been in use since the early 1960s without causing this complication.

The response of the formula manufacturers appears swift. Mead-Johnson introduced a whey-predominant premature infant formula in 1979 (still named Enfamil Premature Formula) (Mead-Johnson, personal communication). Ross Laboratories introduced Similac Special Care in 1980.[15] However, I was unable to determine if the formula changes resulted from the lactobezoar epidemic or previous research on protein quality. Both formulas reduced the casein protein to ~40%.

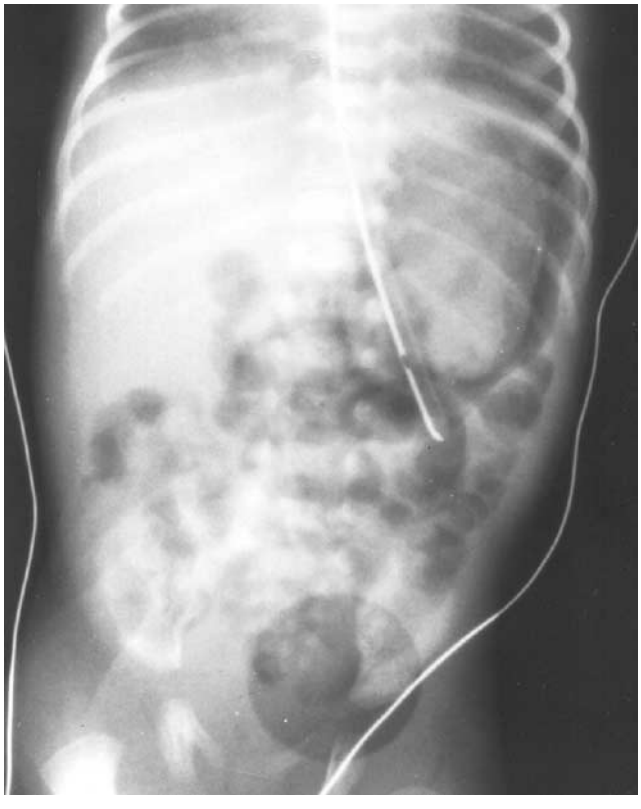

**Figure 2.** Intraluminal mass in stomach. Reproduced with permission (Ref [22]), p426.

In 1982, Schreiner et al.[24] described their experience with lactobezoars using the casein-predominant premature formulas and subsequently using the whey-predominant premature formulas provided by Ross Laboratories and Mead-Johnson. Lactobezoars, for which they now screened, occurred with the original premature formulas, but were no longer found with the new premature formulas. This concept, that the etiology was related to casein content, was strengthened by the fact that breast-milk contains ~20% casein and lactobezoars had not been reported in breast-fed babies at that time. And, across the country, after the formula change, the problem disappeared.

## ERYTHROMYCIN

In February 1999, in Knoxville, TN, there was an outbreak of pertussis involving six newborn infants. Since the most likely source of infection was a hospital worker, the local health department suggested prophylaxis of about 200 infants who may have been exposed to that worker. The prophylaxis was the antibiotic erythromycin as recommended by the American Academy of Pediatrics.[25] Approximately 6 weeks later, local pediatric surgeons had a cluster of seven cases of pyloric stenosis, all of whom had been born in the hospital where the erythromycin was given and all had received the drug.[26] The results of a cohort study showed that none of the infants who had not received erythromycin in that time period developed pyloric stenosis.[27]

In 1976, SanFilippo had reported six infants in a 1-year period who were operated on for pyloric stenosis at the Great Lakes Naval Hospital. Five of the infants received erythromycin. This represented an increase in the incidence of pyloric stenosis from 1 in 400 to 600 infant live births to 1 in 160. The incidence reverted to 1 in 300 after they discontinued the use of erythromycin.[28] The report was not taken very seriously for many reasons. There had been a long experience with erythromycin and this relation had not been previously suggested. The reported cases were not accompanied by a careful cohort study. At that time, intuitively, it did not seem reasonable. The authors reported vomiting occurring 24 to 48 hours after the drug was begun and the presence of a pyloric tumor in 6 to 11 days. It seemed unreasonable that something so clear and closely related temporally would not have been seen either earlier in the history of erythromycin usage or by more observers.

After that report, nothing was heard until 1986 when Stang reported one case of pyloric stenosis in a breast-feeding infant whose mother was receiving erythromycin for mastitis.[29] This baby developed vomiting 5 days after the maternal medication had begun. A 5-year retrospective review of pyloric stenosis at the St. Paul's Children's Hospital in the Twin Cities (St. Paul and Minneapolis) revealed 122 cases of which six had been treated with

erythromycin. Again, in the absence of a careful epidemiological study, the association was questionable and soon forgotten.

Erythromycin was introduced in 1952. This antibiotic was produced by a strain of *Streptomyces erythreus* found in a soil sample from The Philippines. The antibiotic was first used against penicillin-resistant staphylococci and later as an alternative drug to beta-lactam antibiotics for Gram-positive organisms. The drug was used often in pediatric practice after it began being marketed but the occurrence of gastrointestinal discomfort and diarrhea soon limited its use. In the 1970s, there was a renewed interest in the drug for use in chlamydial infections and in the prophylaxis of pertussis.[30] Although not specifically recommended by the CDC or the AAP,[31] many physicians have been treating newborn infants prophylactically if exposed to untreated maternal chlamydial infection.

Hirschsprung, in the late 19th century, gave an accurate clinical and pathological description of pyloric stenosis, and in 1911 Ramstedt revised the surgical treatment to its present form (extramucosal pyloroplasty).[32] The pathology is pyloric circular muscle hypertrophy beginning after birth and progressing to gastric outlet obstruction. Several facts suggest an environmental influence. The hypertrophy occurs after birth within a rather narrow time span. There is a lack of concordance in monozygous twins. And the onset is delayed in premature infants.[33]

One of our modern advantages is being able to diagnose pyloric stenosis in a vomiting baby by ultrasound examination of the pylorus. I remember a family in Columbus, Ohio, whose first male child had pyloric stenosis and was operated on. When the next born child began vomiting at 10 days of age, both the surgeon and I could not feel a pyloric tumor. After several futile visits to the surgeon, I told the parents to wait at home until they could see peristaltic waves crossing the abdomen. When this occurred, the diagnostic tumor was there and the child was operated upon!

The stimulatory effect of erythromycin on the GI tract was first described in 1984. The drug increases antral motility and contraction of the pyloric bulb.[34] The higher doses used for antimicrobial activity cause strong contractions and may result in pyloric hypertrophy.

## PROPYLENE GLYCOL

Propylene glycol was described in 1859 by C. Wurtz who also was the first to prepare ethylene glycol. The compound received little attention until 1932 when Seidenfeld and Hanzlik,[35] looking for a substitute for ethylene glycol, studied its toxicity. At that time, ethylene glycol was being used as a solvent for a bismuth product used to treat syphilis and neurosyphilis. In animal studies, they found the toxicity of propylene glycol less than that of ethylene glycol.[35] Thus began its career as a pharmaceutical solvent.

In 1983, Glasgow et al.[36] reported four infants with serum hyperosmolality ($>300$ mosm/l) related to elevated levels of propylene glycol in the blood. The source was a parenteral multivitamin preparation (MVI-12) containing propylene glycol. As mentioned in the article, the authors had changed multivitamin preparations in their NICU to one containing biotin and had increased the volume of vitamin solution given to provide adequate amounts of the other vitamins.[36] This change led to a 10-fold increase in the propylene glycol dose. The vitamin preparation used was not recommended for patients under 11 years of age.

A follow-up article in 1987 reported 49 infants who had received the excessive amount of propylene glycol and were under 1500 g birth weight. The significant findings, compared to a control group, were elevated serum osmolality, seizures, and intraventricular hemorrhage.[37] The increase in intraventricular hemorrhage may have related to improvements in diagnostic methods between the two periods studied.

## BENZYL ALCOHOL

In 1981, at the SSPR meeting Gershanik et al.[38] reported five preterm infants with severe metabolic acidosis, hepatic and renal failure, and signs of neurological deterioration. A striking clinical aspect was the onset of gasping respirations and the authors named the illness the ''gasping'' syndrome. Unmetabolized benzyl alcohol was found in the urine. An additional 10 babies with the ''gasping'' syndrome died in Oregon that year and were reported by Brown et al.[39] The infants were all of very low birth weight, in the first days of life and had central venous catheters (umbilical artery and/or vein) that were flushed frequently using bacteriostatic normal saline containing 0.9% benzyl alcohol. These cases were reported to the FDA, which recommended the exclusion of benzyl alcohol from flush solutions and diluents used in newborns.[40]

The agent responsible for the toxicity was felt to be benzoic acid. Benzyl alcohol is oxidized to benzoic acid and conjugated with glycine to form hippuric acid in the liver and kidneys. Hippuric acid is excreted in the urine. Benzyl alcohol and its metabolites were elevated in the body fluids of the affected infants. LeBel et al.[41] have shown that the conjugation of benzoic acid to hippuric acid is deficient in premature infants.

Benzyl alcohol is a constituent of jasmine, hyacinth, ylang-ylang oils and balsam. It was originally synthesized in 1853 and has been used as a solvent, a constituent of perfumes, a flavoring agent and as a bacteriostatic agent in injectable medications.[42] In 1942, The United States Pharmacopeia required all medications in multiple dose vials contain a bacteriostatic agent.[43] I have not been able to determine when benzyl alcohol began being used to fulfill this requirement. Why the poisoning became apparent in 1981 is unclear. Umbilical vein catheterization started around 1946 and umbilical artery catheterization around 1949, but was not in routine use until 1972.[44] These central catheters were frequently flushed. The cause of the gasping is also unclear. Gershanik et al.[45] postulate damage by benzyl alcohol or a metabolite to respiratory centers in the pons and lower medulla.

On May 28, 1982, the Food and Drug Administration (FDA) sent letters recommending that flush solutions used in newborns should not contain benzyl alcohol or any other preservative.[46] Subsequent to this notification, manufacturers of multidose solutions containing benzyl alcohol added the warning, ''Not for Use in Newborns'' to labels of commonly used products.

In a report in 1983, the Committee on the Fetus and Newborn and the Committee on Drugs of the AAP pointed out that the removal of benzyl alcohol might have an impact on neonatal mortality if its use and effects were as marked as they seemed from early reports.[47] That possibility gained some credence in a report by Menon et al.[48] The authors reported four infants with metabolic acidosis attributable to benzyl alcohol. Of more interest was their comparison of mortality rates during two 8-month periods, one with and one without benzyl alcohol use. In infants weighing less than 1000 g, 19 of 47 lived for at least 1 month while benzyl alcohol was in use. Following the cessation of benzyl alcohol use, 32 of 48 infants survived at least 1 month. In a more extensive retrospective study, Hiller et al.[49] found a decreased mortality rate (81 vs 46%) and a decreased intraventricular hemorrhage rate (46 vs 19%) in infants less than 1000 g birth weight after removing benzyl alcohol. Their improvement in mortality continued for the subsequent 3 years.

A CDC study revealed that prior to the FDA recommendation to stop the use of benzyl alcohol in small infants, about 70% of hospitals were using benzyl alcohol solutions in the care of sick newborn infants.[50] If we take only the 1 year prior to the warning and estimate an annual birth number of babies 800 to 1000 g ($\sim$5400),[51] calculate the number that may have received benzyl alcohol ($\sim$3780) and factor in an excess mortality rate of 35%, then the annual deaths attributable to benzyl alcohol may have been as high as 1890 infants. We do not know how many years benzyl alcohol had a significant effect. However, the effect on mortality was not verified in the study of Jardine and Rogers[52] published in 1989. Their study showed a slowly declining mortality rate, which they felt reflected general improvement in care methods and not a sudden change as might be expected with the removal of benzyl alcohol. They did show a significant decline in intraventricular hemorrhage and an abrupt disappearance of kernicterus at autopsy.

The effect of removing benzyl alcohol on kernicterus was reasonable in that benzoate, the metabolite of benzyl alcohol, had long been known to displace bilirubin from albumin.[53] Cronin et al.[54] also noted the disappearance of kernicterus from their autopsy service over the year that benzyl alcohol was removed. However, in their study, comparison of 29 kernicteric infants to 28 contemporaneous controls without kernicterus showed no difference in the exposure to benzyl alcohol.

So we are left with many questions. It appears that the removal of benzyl alcohol from neonatal care has eliminated the ''gasping'' syndrome and may partially explain the decline in intraventricular hemorrhage rates since 1982. Whether we have affected mortality and kernicterus rates is unknown. It is ironic that benzoate-containing drugs were cautioned against in 1971.[53]

The concern about benzyl alcohol resurfaced when doxapram, produced in Canada, began being used for apnea in premature infants.[55]

## INTRAVENOUS (I.V.) VITAMIN E

In 1949, before the implication of oxygen as a cause of retrolental fibroplasia (RLF), Owens and Owens[56] postulated that RLF was related to vitamin E deficiency. Their rationale for suspecting vitamin E was that the vitamin concentration was known to be low in the serum of premature infants, declined over the first few weeks of life (at the same time RLF was developing), and was not one of the supplemented vitamins in neonatal care.

The discovery of vitamin E dated back to 1922 when Evans and Bishop identified an unknown dietary factor in wheat germ and lettuce that affected reproduction in the laboratory rat. In 1925, the factor was designated vitamin E. The molecular structures of the vitamin and its synthesis were elucidated by 1938[57] and that year Widenbauer reported its apparent growth-promoting effect in premature infants.[58]

Although the early results of the Owens' trial of vitamin E to prevent RLF were encouraging, subsequent trials were not. The issue was dormant until 1974 when Johnson et al. reported a preliminary study of intramuscular alpha tocopheryl acetate, showing a trend toward decreasing the severity of RLF. This and subsequent studies are summarized in our chapter, ''Vitamin E in Neonatology'' published in 1986.[59]

Although further trials during the 1970s on the efficacy of vitamin E in ameliorating RLF were conflicting, many nurseries administered the vitamin orally to their premature infants. Since many of the very small infants were not fed orally in the first week of life, and since intramuscular injections were traumatic, an intravenous form of vitamin E was sought. In December 1983, E-Ferol Injection for intravenous administration was introduced by O'Neal, Jones and Feldman Pharmaceuticals of St. Louis, MO (Figure 3). The preparation had been formulated by Carter-Glogau Laboratories of Glendale, AZ. Although there was no mention of RLF in the ''Indications'' section of the packaging, in the ''Clinical Pharmacology'' section it was stated, ''Reports in the literature indicate that substantial doses of Vitamin E will reduce the severity of retrolental fibroplasia in neonatals, which are administered oxygen because of their low birth weight, under 1500 grams.'' The new product was eagerly accepted by neonatologists across the country. This was the beginning of a tragedy that led to the death of about 40 infants, dissolution of two pharmaceutical company and imprisonment of three executive officers.

Within months of E-Ferol's introduction to neonatal care, neonatologists began to note clusters of premature babies who developed hepatomegaly, thrombocytopenia, cholestatic jaundice, ascites, and azotemia. These cases were reported to the CDC,

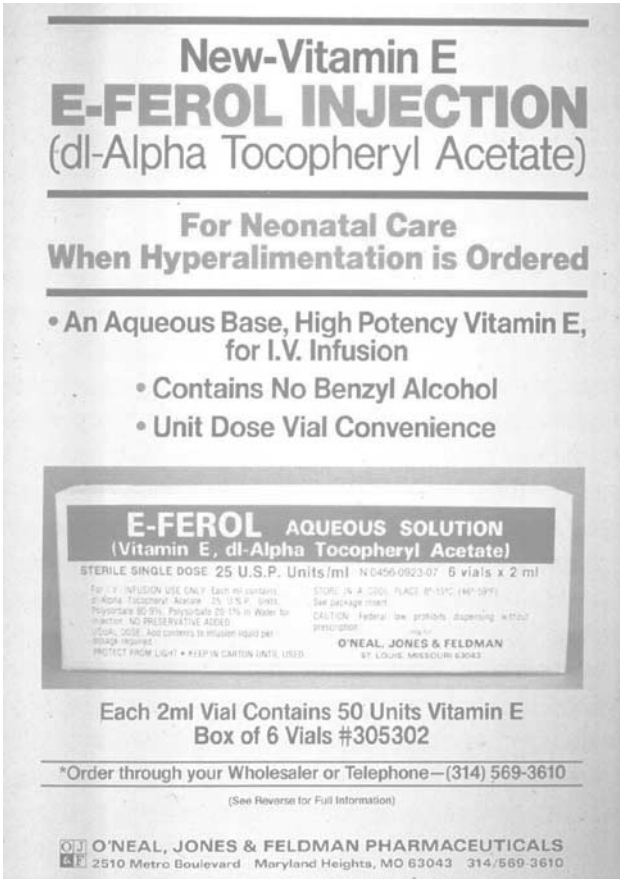


**Figure 3.** Advertisement for E-Ferol. Brochure mailed to neonatalogists.

beginning March 9, from Spokane WA, Knoxville, TN and Cincinnati, OH and were first described in print on April 13.[60] On April 16, 1984, the FDA issued an Urgent Class I Drug Recall letter, indicating that the drug was being voluntarily recalled by the company. Also in the letter it was noted that the E-Ferol Aqueous Solution ''has not been approved by FDA''.

On July 9, 1987, a federal grand jury indicted three pharmaceutical company executives involved in the production and marketing of E-Ferol. Reports from the trial and follow-up events in the St. Louis Post Dispatch from June 15, 1988 to October 19, 1993 indicate that the executives purposefully excluded RLF from the ''Indications'' section of the drug information pamphlet, knowing that such an indication would require FDA approval, whereas listing only nutritional indications might bypass this requirement. Their clear purpose for the development of the intravenous preparation, however, was to market the drug for the prevention or amelioration of RLF. The trial also revealed that the vice president of the distributing pharmaceutical company was aware of the first infant deaths in Washington state and their possible relation to E-Ferol, but withheld this information when queried by health professionals. In January 1989, three executives involved in the case were sentenced to jail sentences of 6 months.

The cause of the illness in the affected infants has never been proven, but an elevated level of the solubilizer, polysorbate, was found in the ascitic fluid from one infant[61] and polysorbate 80 appears to be especially toxic in cell culture and animal studies.[62]

Polysorbate 80 or Tween 80 has been used in foods and drugs since the 1950s. The compound's solubility in water, alcohol and various oils make it an ideal emulsifier and dispersing agent for medicinal products designed for internal use.[63] Toxicity studies of i.v. injection in adult rats showed an $LD_{50}$ of 0.7 ml/kg, a relatively large dose, which allayed worries about toxicity.[64] Metabolism to the polyoxyethylated compound and renal excretion are quite rapid in the adult animal. Previous studies of its toxicity did not include newborn infants. However, toxicity had not been previously noted in newborns receiving other drugs containing polysorbate 80 and, in this case, the problem was probably increased concentration of polysorbate 80 needed to solubilize the vitamin E. In fact, the president of Carter-Glogau Laboratories, Inc., Ronald M. Carter said, in a communication to James B. Madison, the vice president of O'Neal, Jones and Feldman Pharmaceuticals, ''Solubilization of vitamin E in a water-miscible base requires extraordinary amounts of surfactants and other carriers. The administration of this product intravenously in neonatals without appropriate clinical work concerning toxicity will undoubtedly lead to an exposure in terms of product liability which neither you nor we may wish to assume. After all, one neonatal death is one too many''.[65] But they proceeded and used 10 times as much polysorbate 80 as had been used in previous formulations.[64]

The executives argued that they were able to introduce this new formulation of vitamin E without FDA approval since, in 1962, an amendment was passed excluding new formulations of previously approved drugs from FDA review. Following this catastrophe, the rules were amended to include review of all new drugs or drug formulation changes.

## STEROIDS

There is controversy about the relation between steroid therapy (used for the treatment or prevention of bronchopulmonary dysplasia (BPD)) and cerebral palsy. This purported relation led the AAP, Committee on Fetus and Newborn,[66] to recommend in 2002 that ''the use of corticosteroids should be limited to exceptional clinical circumstances''. Barrington[67] states in his systematic review of the literature, ''This analysis strongly suggests that the single most effective intervention which could currently be introduced for improving neuro-developmental outcomes of extremely low birth weight infants would be to immediately abandon the use of postnatal steroids for chronic lung disease''. If steroid use is an error, it is certainly a large one for this treatment has been common in most neonatal intensive care units around the world. If the relation between steroid treatment and cerebral palsy is not confirmed in further studies, then the error may be in not using steroids.

BPD was first described by Northway et al.[68] in 1967. With improvements in infant ventilators, more small infants survived and more infants had chronic lung disease. BPD was (and still is) the greatest disappointment in neonatal care. In 1971, I moved to the Medical College of Georgia and attended regularly in the NICU. At the beginning of each month of attending, I would ask, with dread, how many patients I had with severe BPD. I was ready to accept any treatment and remember exactly when I started using corticosteroids. The year was 1985 and Dr. Spencer Brudno had just joined our faculty. In January, he had co-authored with Avery, Fletcher, and Kaplan an article describing the beneficial results of dexamethasone in infants with BPD.[69] The treatment caused improvement in pulmonary compliance and rapid weaning from the respirator. This early study, and the few preceding it, did not provide developmental follow-up data.

The story of the discovery of cortisone is multifaceted. The following notes are taken from Witzmann's[70] delightful book, *Steroids: Keys to Life*. In 1812, Chevreul isolated a fat in gall stones that remained solid at high temperatures. He named the substance chole (gall) stereos (solid), cholesterol. Cholesterol was the first steroid compound described and little was made of it for 100 years. In 1849, Berthold elucidated the concept of internal secretion organs and hormones. He castrated cocks and later implanted a testis in the abdominal cavity. As he described the animals after the transplant, ''In their general behavior, these four cocks (b,e,c,f) displayed the nature of uncastrated animals: they crowed quite soundly, often engaged in fights with each other and with other young cocks, and showed the usual inclination toward the hens; moreover, their combs and wattles developed as in ordinary cocks.'' This study demonstrated the effect of gland secretions independent of direct vascular or nervous system connections; that is, endocrine secretions. That same year Addison described his ''bronzed skin'' disease and related the condition to the adrenal gland. In 1859, Brown-Séquard adrenalectomized animals leading to their death in 24 hours. This result established the importance of the adrenal gland but, at that time, the theory was that the gland cleared toxins from the blood. In 1889, Brown-Séquard demonstrated that glandular extracts were active by treating himself with a testicular extract preparation. The results were dramatic! In 1930, Swingle and Pfiffner extracted active compounds from the adrenal cortex and Kendall, at the Mayo Foundation, established their steroid structure and, in 1948, purified compound E (cortisol). Dr. Hench at the Mayo clinic believed that rheumatoid arthritis was caused by adrenal insufficiency and used Kendall's compound E to treat several patients. The near miraculous results were presented in 1949. The final hurdle was the chemical synthesis of cortisol. The intense competition of scientists and pharmaceutical companies toward this goal is described by Djerassi[71] in his book *The Pill, Pigmy Chimps, and Degas' Horse*. The Upjohn company succeeded in 1951 and cortisone was soon available for the treatment of many illnesses.

I remember little concern about the use of dexamethasone in infants with BPD. Perhaps my attitude was related to frustration with this iatrogenic nightmare. In 1988, Cummings et al.[72] reported the effects of a 42-day course of dexamethasone in 36 infants who were ventilator dependent at 2 weeks of life. The 15-month follow-up exam showed no neurological abnormalities in the treated group whereas 40% of the survivors from the control group had truncal hypotonia or cerebral palsy. A multicenter European study with 4-year follow-up showed no difference in neurodevelopmental outcome among the randomized groups.[73] Yeh et al.[74] in 1998 and O'Shea et al.[75] in 1999 showed an increase in neuromotor dysfunction and cerebral palsy in dexamethasone-treated infants. An excellent review of the many aspects of this question is presented by Watterberg.[76]

Evaluating this subject as a possible error is difficult at this time and this discussion is not complete. Infants with BPD are at risk for poor neurodevelopmental outcome regardless of the treatment. The study results have been varied. The concern is reasonable since corticoid therapy has a long history of complications including decreased brain growth in animals.[77] The interesting point to me is the ease with which we have been able to avoid steroid therapy since these concerns arose. Obviously, in most cases, little has been lost.

## CAUSES OF ERRORS

In all these episodes, excluding the vitamin E tragedy, the motivation leading to harmful treatments was an honest desire to improve the care of infants. This desire has always led to therapeutic creativity and risk taking which, in many other instances, has been beneficial. It is helpful to analyze how this creativity goes awry. Most ideas for new treatments are based on seemingly appropriate premises. A possible exception among the errors discussed here is Epsom salts enemas for respiratory distress, which was based on erroneous interpretation of pathological data. A more frequent cause of difficulty is a lack of knowledge of neonatal physiology. The use of lowered thermal environment and initial thirsting and starving illustrate such lack of knowledge. The formula errors (pyridoxine deficiency and chloride deficiency) fit well here. The relation of sulfisoxazole and kernicterus was established before the displacement of bilirubin from albumin by drugs had been shown in newborns. The use of chloramphenicol preceded knowledge of its metabolism and excretion in premature infants. Bathing with hexachlorophene preceded the knowledge of the degree of transdermal absorption of agents in premature infants.

Another cause of problems is the lack of, or inadequate design of, pilot studies. This is well illustrated in the cases of the Bloxsom air-lock and gastrostomy for feeding, which were proposed from uncontrolled studies with inadequate numbers of infants.

The presumption of safety in the absence of testing on premature infants is an error, which resulted in RLF because of supplemental oxygen use and, less directly, benzyl alcohol, propylene glycol and polysorbate toxicity. Reliance on animal or adult studies is inappropriate.

What I look on as inappropriate procedural changes led to the episodes of methemoglobinemia caused by aniline dye markings on diapers, the ''sweating'' syndrome with the laundry use of pentachlorophenol and jaundice caused by phenolic compounds used for equipment cleaning.

When a therapeutic initiative is begun, it may proceed out of control because of publicity. This was certainly the case with the Bloxsom air-lock and Epsom salts enemas. In these instances, the attendant publicity, rather than careful study, led to their rapid dissemination and use. The press' lack of sophistication in scientific evaluation was, perhaps, as striking as physicians' gullibility. Similarly, authoritative opinions have an unjustified credibility. Lowered thermal environment started with the problem of overheating in early incubators and was reinforced when the data of Blackfan and Yaglou[78] showed no relation of mortality to body temperature. However, their study excluded babies who died early after admission and included older babies, and therefore did not answer the question of ideal thermal environment. What was most influential was the opinion of the Boston physicians that premature infants normally maintained a lower body temperature. The supplemental oxygen error was partly based on the opinion that periodic breathing indicated a state of noncyanotic hypoxia. Initial thirsting and starving originated with the problems of feeding small babies, but was then justified by the opinion that these infants needed to excrete excess fluid retained from intrauterine life.

Many of these events, regardless of the process error, have resulted from the use of pharmacological agents (synthetic vitamin K, sulfisoxazole, chloramphenicol, novobiocin, hexachlorophene, erythromycin). New pharmacological agents have been and will continue to be a danger in neonatology. Many adverse effects may not be seen in small population studies performed for licensing. Manufacturers often prefer to avoid the issue and exclude neonates from the drug's indications for use. But that exclusion has little effect because the ''off-label'' use of drugs (in a formulation or dosage or for a condition not covered by licensure) in neonatology is extremely common.[79]

## LESSONS LEARNED

Everyone will extract different lessons from these tales. Certainly, we should be more aware of neonatal physiology when we consider new treatments. We should not presume safety unless proven by adequate studies. We should be wary of all procedural changes. Hospital administration should ensure the education of ancillary personnel about the susceptibilities of infants so that no change in hospital procedure can occur without the consideration of its effect on babies. And we should be skeptical of authoritative opinions. This requirement is difficult since most of us are authoritarian by nature and experience. As Dr. Silverman states, ''Physicians depend, more than ever, on the judgments and opinions of authorities because of an exponential increase in scientific information and an increase in the complexity of medicine''.[80] For those of us who may be the lecturers, he continues, ''Authoritative lecturers should stimulate their listeners to responsible contemplation of incomplete evidence, instead of irresponsible, unrestrained action.''

When should we incorporate new therapies into our daily practice? Over the years, I have tried avoiding new therapies until several publications have suggested their efficacy and safety. But in today's medical environment that method is too simplistic. How do I know my literature review is accurate? How do I answer the question, ''How much evidence is enough?'' Each individual or group practice should answer these questions before embarking on new therapies. Sinclair[81] describes the process as consisting of five key elements; asking a focused clinical question, searching for high-quality evidence, appraising the evidence's validity, extracting the data and applying the results to patient care. The complexity of each of these steps is daunting. As he states, many physicians feel unprepared for these steps and believe that the introduction of evidence-based practice guidelines (by expert committees) is best. The pros and cons of practice policies and the application of policies to decision-making in patient care are discussed by Eddy.[82,83]

The greatest hazard since the ''Hands Off'' years has been unexpected reactions to drugs. Since our information is never complete, continuing surveillance of drug effects is vital, especially those used ''off-label''. As stated by the Committee on Drugs, AAP,[84] ''Physicians who choose to prescribe a medication with limited pediatric data have a public and professional responsibility to assist in the systematic development of the information about that drug for the benefit of other patients''. The pharmacokinetic properties of drugs and additives should be known in premature infants before their general clinical use.

Inevitably, other errors will happen. We cannot prevent the use of new treatments and nonrandomized trials will continue. In these instances, ''the number of injured can always be reduced by using the hedging strategy of concurrent controls'',[85] where half the patients are not exposed to the unexpected hazard.

I hope that by studying these mistakes, we will avoid some future problems or at least recognize the problems early in their course.

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